High-resolution myogenic lineage mapping by single-cell mass cytometry.

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Funding Grants: Mass Cytometry to Delineate the Human Muscle Stem Cell Hierarchy and Dysfunction in Aging

Public Summary:
Adult muscle stem cells are the driving force in skeletal muscle regeneration, a dynamic process during which the state and identity of the cells involved changes over time. Mostly dormant in healthy individuals, muscle stem cells awaken in response to muscle damage to produce specialized progeny, muscle progenitor cells, which will repair the damaged muscle. While the identity of muscle stem cells has been previously established, muscle progenitor cells, which represent a stage in between the stem cell and the mature muscle cell, have not yet been identified. A major challenge in their identification has been a lack of tools to dissect the cellular complexity of skeletal muscle, emphasizing the importance of single-cell studies. Here, we capitalized on single-cell mass cytometry, a new technology that allows the identification of new cell populations within complex tissues, to capture stem cell decisions in skeletal muscle. We discovered two surface markers whose combined expression enables the identification and isolation of muscle progenitor cells and resolved the intermediate stages of myogenesis during muscle regeneration at an unprecedented level of detail. In the blood, the discovery and isolation of stem and progenitor cells many decades ago was instrumental for understanding their role in regeneration and elucidating the mechanisms of blood cancers, which led to the development of therapies for several blood diseases. Similarly, the elucidation of muscle progenitor cells has the potential to reveal the key events that regulate muscle regeneration and unravel the mechanisms of cancer, promoting the development of new therapies for muscle diseases and aging.

Scientific Abstract:
Muscle regeneration is a dynamic process during which cell state and identity change over time. A major roadblock has been a lack of tools to resolve a myogenic progression in vivo. Here we capitalize on a transformative technology, single-cell mass cytometry (CyTOF), to identify in vivo skeletal muscle stem cell and previously unrecognized progenitor populations that precede differentiation. We discovered two cell surface markers, CD9 and CD104, whose combined expression enabled in vivo identification and prospective isolation of stem and progenitor cells. Data analysis using the X-shift algorithm paired with single-cell force-directed layout visualization defined a molecular signature of the activated stem cell state (CD44+/CD98+/MyoD+) and delineated a myogenic trajectory during recovery from acute muscle injury. Our studies uncover the dynamics of skeletal muscle regeneration in vivo and pave the way for the elucidation of the regulatory networks that underlie cell-state transitions in muscle diseases and ageing.